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(54) 12-AZAPROSTAGLANDINS

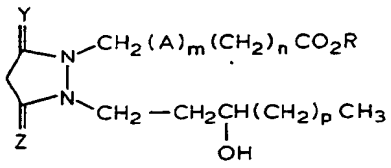
(71) We, BEECHAM GROUP LIMITED, a British Company of Beecham House, Great West Road, Brentford, Middlesex, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to compounds having pharmaceutical activity, to a process for their production, to intermediates useful in that process and to pharmaceutical compositions containing the active compounds.

More specifically, this invention relates to 12-azaprostaglandins, to the preparation of such compounds *via* novel carboxylic acids or their esters and to pharmaceutical compositions containing the cyclic amides and amines.

Natural prostaglandins and analogues thereof are known to possess a wide variety of pharmacological activities.

Offenlegungsschrift No. 2,323,193 discloses that pyrazolidine derivatives of the formula (I):



(I)'

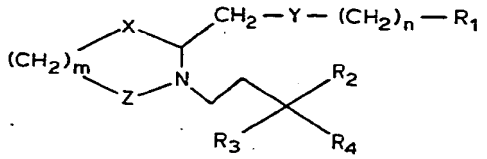
wherein A is CH=CH or C≡C; R is H, an alkali metal, an amine salt, or a hydrocarbon or chlorohydrocarbon residue containing no more than 12 carbon atoms; m is 0 or 1; n is 0—6; p is 0—6; and Y and Z are 0 or H_2 except that Y and Z are not both 0;

have similar biological properties to the prostaglandins or are antagonists of prostaglandins.

A paper by Bolliger and Muchowski (Tet. Letters, 1975, 2931), describes the preparation of 11-deoxy-8-azaprostaglandin E_1, but states only that one epimer thereof was more active in several biological assays than the other epimer.

A novel class of compounds has now been discovered within which useful pharmacological activity is displayed. For example compounds within this class have anti-gastric secretion activity, cardiovascular activity e.g. anti-hypertensive activity, platelet aggregration inhibition activity, affect the respiratory tract e.g. bronchodilator activity, and have antifertility and smooth muscle activity. In general it may be said that compounds within this class have a range of pharmacological activities similar to those shown by the natural prostaglandins, but that these activities tend to be rather more selective.

Accordingly the present invention provides a compound of the formula (I):

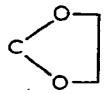


(I)

wherein:
X is CO, protected CO, CROH in which R is hydrogen or C_{1-4} alkyl and in which the OH moiety may be protected;
Y is CH_2CH_2 or *cis*- or *trans*-CH=CH;
Z is CO or CH_2;
n is 1 to 8;
m is 1, 2 or 3;
R_1 is hydrogen, CH_2OH, CH_2IH in which the OH moiety is protected, CO_2W wherein W is hydrogen or CO_2W represents an ester group in which the ester moiety contains from 1 to 12 carbon atoms, or $CONH_2$;
R_2 is hydrogen, C_{1-4} alkyl, or taken together with R_3 and the carbon atom to which it is attached represents a carbonyl group;
R_3 is hydrogen, hydroxy or protected hydroxy;
R_4 is hydrogen or C_{1-3} alkyl;
and salts thereof.

In formula (I), often n will be 3 to 8, R_2 will be a hydrogen atom or methyl group, or taken together with R_3 and the carbon atom to which it is attached will represent a carbonyl group, and X will be CO, CROH in which R is hydrogen or C_{1-4} alkyl and in which the OH moiety may be protected.

Suitable protected CO groups X include groups formed by conventional carbonyl addition and condensation reactions such as ketals, thioketals, hemithioketals, oximes, semicarbazones and hydrazones. Of such groups often the ketal type derivatives will be most useful, for example when X is a group



Examples of suitable groups X include CO, CHOH, $C(CH_3)OH$ and $C(C_2H_5)OH$. Preferably X is CO, CHOH or $C(CH_3)OH$, most preferably CO. Similarly it is often preferred that Y is CH_2CH_2 and also that Z is CO.

While n may be 1 to 8, n is most suitably 1 to 5. Within this narrower range, the preferred values for n include 3, 4 and 5, 3 being the most preferred. Thus it will be seen that the α side chain of the compounds of the formula (I) will often be of the formula $(CH_2)_{n^1}R^1$ wherein n^1 is 6, 7 or 8, preferably 6.

We believe that the most valuable compounds of the formula (I) are given when m is 1 and also when m is 2. Further, we have found that in some pharmacological test systems compounds wherein m is 1 demonstrate a rather higher potency than the corresponding compounds wherein m is 2.

Suitable protected hydroxy groups include readily hydrolysable groups such as acylated hydroxy groups in which the acyl moiety contains 1 to 4 carbon atoms, for example the acetoxy group, and hydroxy groups etherified by readily removable inert groups such as benzyl groups. Preferably the hydroxy groups in formula (I) are unprotected.

Suitable groups R_1 include hydrogen, CH_2OH, CO_2H and the methyl, ethyl, propyl, butyl, pentyl, hexyl, phenyl, benzyl or tolyl ester of the said CO_2H acid group. Normally however R_1 will be hydrogen, CH_2OH, CO_2H or a C_{1-4} alkyl ester of the said CO_2H acid group.

Of the variants possible for R_2, the most suitable include hydrogen, methyl and ethyl, and of these methyl and ethyl are often preferred. Most usually R_2 will be methyl.

R_3 is hydrogen, hydroxy or protected hydroxy. Suitable protected hydroxy groups R_3 have of course been described above. Preferably R_3 is hydrogen or hydroxy, most preferably hydroxy.

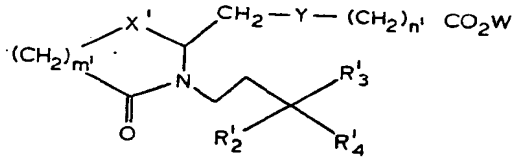
R_4 is hydrogen or a C_{1-9} alkyl group. Suitable examples of R_4 include C_{4-9} alkyl groups which may be straight chain alkyl groups, such as *n*-butyl, *n*-pentyl, *n*-hexyl and *n*-heptyl, or may be alkyl groups, such as the aforenamed alkyl groups, branched by one or two methyl groups (at the same or different carbon atoms).

Thus for example R_4 may be a group CH_2R_5, $CH(CH_3)R_5$ or $C(CH_3)_2R_5$, wherein R_5 is a straight chain alkyl group such that the carbon content of the resultant group R_4 is 4 to 9. Suitably R_5 is *n*-butyl or *n*-pentyl.

In general preferred groups R_4 include straight chain pentyl, hexyl and heptyl groups. Of these, straight chain hexyl is often the most useful.

The compounds of the formula (I) may form conventional acid salts when W is hydrogen. Such salts include those with alkali and alkaline earth metals, suitably sodium and potassium, and ammonium and substituted ammonium salts. Also, when Z is CH_2, the resultant amine of the formula (I) may form acid addition salts with conventional pharmaceutically acceptable acids. Examples of such acids include hydrochloric, hydrobromic, phosphoric acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic acids.

A group of compounds of particular interest within formula (I) include compounds of the formula (II):



(II)

wherein:
X^1 is CO, or CHOH or $C(CH_3)OH$ in which the OH moieties may be protected;
m^1 is 1 or 2;
n^1 is 1 to 5;
R^1_2 is hydrogen or C_{1-4} alkyl;
R^1_3 is hydrogen, hydroxy or protected hydroxy;
R^1_4 is hydrogen or C_{4-9} alkyl; and
Y and W are as defined in formula (I): and salts thereof.

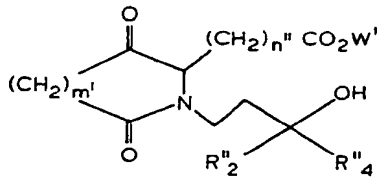
In formula (II), suitable examples of X^1 include CO, CHOH and $C(CH_3)OH$. Normally it is preferred that X^1 is CO, Y is CH_2CH_2, m^1 is 1, and n^1 is 3 or 5 (most preferably 3).

Suitably R^1_2 is hydrogen, methyl or ethyl. Of these three values, R^1_2 is most suitably methyl or ethyl, preferably methyl. Similarly, suitably R^1_3 is hydrogen or hydroxy, preferably hydroxy.

Suitable and preferred straight chain and branched alkyl groups R^1_4 include those previously described as suitable and preferred for the group R_4 when R_4 is a C_{4-9} alkyl group. Such preferred groups R^1_4 include straight chain pentyl, hexyl and heptyl, and of these normally the most useful is straight chain hexyl.

Of the variants possible for W as defined in formula (I), normally we prefer that W is hydrogen or a C_{1-4} alkyl group such as the methyl or ethyl groups.

Thus is can be seen that within formula (II) there is a sub group of particular utility of the formula (III):



(III)

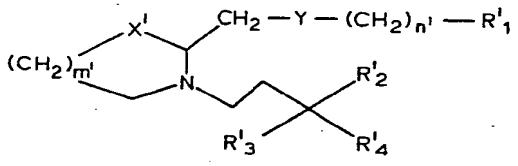
wherein:
m^1 is 1 or 2;
n^{11} is 6 or 8;
R^{11}_2 is hydrogen, methyl or ethyl;
R^{11}_4 is *n*-pentyl *n*-hexyl or *n*-heptyl; and
W^1 is hydrogen or C_{1-4} alkyl; and salts thereof.

In formula (III), m^1 is preferably 1 and n^{11} is preferably 6. Similarly R^{11}_2 is most usefully methyl or ethyl (preferably methyl), and R^{11}_4 is preferably *n*-hexyl. Lastly in formula (III) W^1 is most suitably a C_{1-4} alkyl group such as the methyl or ethyl group.

The most useful compounds within formula (III) include the following:

2 - (6′ - Ethoxycarbonyl - *n* - hexyl) - 1 - (3″ - hydroxy - 3″ - methyl - *n* - nonyl)-pyrrolidin - 3,5 - dione.
2 - (6′ - Ethoxycarbonyl - *n* - hexyl) - 1 - (3″ - hydroxy - 3″ - methyl - *n* - octyl)-pyrrolidin - 3,5 - dione.
2 - (6′ - Ethoxycarbonylhexyl) - 1 - (3″ - hydroxy - 3″ - methyl - *n* - decyl)-pyrrolidin - 3,5 - dione.
2 - (6′ - Ethoxycarbonyl - *n* - hexyl) - 1 - (3″ - hydroxy - 3″ - ethyl - *n* - nonyl)-pyrrolidin - 3,5 - dione.

In formula (I), when Z is CH_2 a useful group of compounds includes those of formula (IV):



(IV)

wherein:
X^1, Y, m^1, n^1, R^1_2, R^1_3 and R^1_4 are as defined in formula (II); and
R^1_1 is CH_3, CH_2OH or CH_2OH in which the OH moiety is protected;
and salts thereof.

X^1 in formula (IV) may be CO, CHOH or $C(CH_3)OH$ in which the OH moiety may be protected. In general it may be said that X^1 is most usefully CHOH or $C(CH_3)OH$. Also Y is preferably CH_2CH_2, and n^1 is preferably 3 or 5 (most preferably 3).

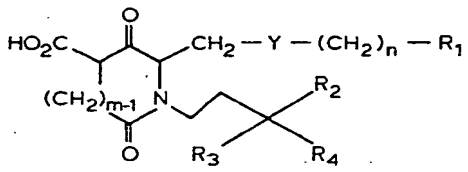
Suitable examples of the group R^1_2 include hydrogen, methyl and ethyl, preferred examples include hydrogen and methyl. In the same way, suitable examples of R^1_3 include hydrogen and hydroxy.

Suitable and preferred examples of the group R^1_4 include those described for R^1_4 in relation to formula (II).

R^1_1 may be CH_3, CH_2OH or CH_2OH in which the OH moiety is protected. When R^1_1 is CH_3, then often R^1_2 and R^1_3 will be hydrogen, R^1_4 will represent a straight chain pentyl, hexyl or heptyl group, and X^1 will be CHOH or $C(CH_3)OH$. In the same way when R_1 is CH_2OH (or less preferably CH_2OH in which the OH moiety is protected), X^1 will normally be CHOH or $C(CH_3)OH$, R^1_2 will be hydrogen, methyl or ethyl, preferably hydrogen or methyl, and R^1_3 will be hydrogen or hydroxy.

It will of course be realised that the compounds of the formula (I) have asymmetric centres, and thus are capable of existing in a number of stereoisomeric forms. The invention extends to each of these stereoisomeric forms, and to mixtures thereof. The different stereoisomeric forms may be separated one from the other by the usual methods.

The present invention also provides a process for the preparation of a compound of the formula (I), which process comprises decarboxylating a compound of the formula (VI):



(VI)

wherein m, n, Y, R_1, R_2, R_3 and R_4 are as defined in formula (I), to yield a compound of the formula (I) wherein X and Z are CO; and thereafter if necessary converting X in the thus formed compound to protected CO by conventional methods, or to

CROH by reduction when R is hydrogen or by reaction with a C_{1-4} alkyl Grignard reagent or C_{1-4} alkyl metallic complex when R is C_{1-4} alkyl, and then optionally protecting the CROH hydroxy moiety; and thereafter if necessary reacting a thus formed compound of the formula (I) wherein Z is CO with a vigorous reducing agent to convert it into the corresponding compound wherein Z is CH_2 and wherein other carbonyl functions present in the chosen compound of the formula (I) are reduced; and thereafter if necessary oxidising one or more of these reduced carbonyl functions back to carbonyl functions.

The decarboxylation reaction may be brought about under basic, acid or neutral conditions in conventional manner. For example when $m=1$ the reaction is conveniently effected by heating the chosen compound of the formula (VI) in a suitable solvent such as toluene or xylene.

The conversion of a compound of the formula (I) wherein X is CO to the corresponding compound wherein X is protected CO may be carried out under conventional reaction conditions for, for example, carbonyl addition and condensation reactions.

The conversion of a compound of the formula (I) wherein X is CO to the corresponding compound wherein X is CHOH may be carried out by conventional methods for reducing a ketone to an alcohol, for example by sodium borohydride reduction.

The conversion of a compound of the formula (I) wherein X is CO to the corresponding compound wherein X is CROH in which R is C_{1-4} alkyl may be carried out by conventional Grignard or alkyl metal, (suitably alkyl lithium) reactions.

After the decarboxylation reaction the group W may be varied in compounds wherein R_1 is CO_2W by conventional de-esterification and/or esterification reactions. Similarly protected CROH and R_3 hydroxy moieties may be deprotected by conventional methods. For example, when R_3 is a benzyloxy group, the benzyl group may readily be removed by hydrogenolysis. Thus it may be seen that 'protected hydroxy' compounds of the formula (I) are useful intermediates in the preparation of the corresponding 'free hydroxy' compounds of the formula (I).

When W is hydrogen, salts of compounds of the formula (I) may be prepared in conventional manner, for example by reacting the chosen compound of the formula (I) with the required base.

Similarly compounds of the formula (I) wherein R_1 is $CONH_2$ may be prepared by conventional methods from other compounds of the formula (I), for example by ammonolysis of the corresponding compound wherein R_1 is an ester group CO_2W.

Also compounds of the formula (I) wherein R_3 is OH may be prepared by conventional reduction or Grignard reactions on the corresponding compound wherein CR_2R_3 is a carbonyl group.

The reduction of a compound of the formula (I) wherein Z is CO to give the corresponding compound wherein Z is CH_2 requires a vigorous reducing agent.

Suitable such reagents include lithium aluminium hydride and its chemical equivalents. The reaction conditions used for this reaction are generally those conventionally associated with the use of lithium aluminium hydride.

Due to the potency of the reducing agent used to effect the desired $Z=CO$ to $Z=CH_2$ conversion in a compound of the formula (I), if the starting compound of the formula (I) wherein $Z=CO$ contains a carbonyl function in addition to that of Z, then this additional carbonyl function will also be reduced. Accordingly when compounds of the formula (I) wherein Z is CH_2 are required in which such other carbonyl functions are present, they must be prepared from corresponding compounds of the formula (I) wherein Z is the CH_2 and the said other carbonyl functions are reduced, by selective oxidation. Examples of such selective oxidation are given in the following three paragraphs.

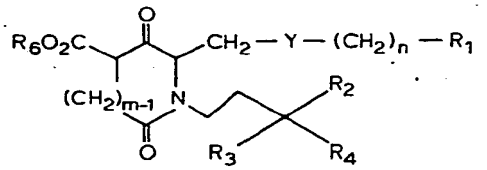
A compound of the formula (I) wherein Z is CH_2 and X is CO may be prepared by the oxidation of the corresponding compound wherein X is CHOH. A suitable oxidising agent for this reaction is a chromium trioxide-pyridine mixture in methylene chloride.

A compound of the formula (I) wherein Z is CH_2 and R_1 is a group CO_2W may be prepared by the oxidation and optional subsequent salification or esterification of the corresponding compound of the formula (I) wherein R_1 is CH_2OH. A suitable oxidising agent for this reaction is a chromic acid-acetic acid mixture.

A compound of the formula (I) wherein Z is CH_2 and CR_2R_3 represents a carbonyl group may be prepared by the oxidation of the corresponding compound of the formula (I) wherein CR_2R_3 is a CHOH group. A suitable oxidising agent for this reaction is a chromium trioxide-pyridine mixture in methylene chloride.

It will be realised that the optional interconversions described above for compounds of the formula (I) wherein Z is CO after their preparation by decarboxylation may just as readily be carried out with compounds of the formula (I) wherein Z is CH_2 after *their* preparation by reduction.

It is frequently convenient to generate the compound of formula (VI) *in situ* from a corresponding ester of the formula (VII):

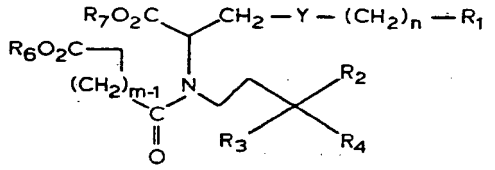


(VII)

wherein CO_2R_6 is an ester group in which the ester moiety contains from 1 to 12 carbon atoms. In such a case R_6 is preferably a benzyl group or a lower alkyl group such as methyl or ethyl. It has been found that often it is sufficient to bring about de-esterification and subsequent decarboxylation in the chosen compound of the formula (VII) simply to leave the compound standing in an inert solvent, for example overnight. Otherwise the desired de-esterification and decarboxylation in the chosen compound of the formula (VII) can be brought about by treatment with, for example, lithium iodide dihydrate and collidine in anhydrous solvents. In cases where m=1, the compound of the formula (VII) can also for example be de-esterified and decarboxylated by heating the compound alone or preferably, in a high boiling solvent such as toluene or xylene.

It will be appreciated that compounds of the formulae (VI) and (VII) are useful intermediates and as such form an important aspect of this invention.

The compounds of formula (VII) may be prepared by the ring closure of the corresponding diester of formula (VIII):



(VIII)

wherein m, n, Y, R_1, R_2, R_3 and R_4 are as defined in formula (I), R_6 is as defined in formula (VII), and R_7 is a group such that CO_2R_7 is an ester group in which the ester moiety contains from 1 to 12 carbon atoms.

In the processes of the invention the group R_1 in the intermediates of formula (VI), (VII) and (VIII) will often represent an ester group CO_2W, and if for example acids of the formula (I) (wherein R_1 is CO_2H) are required they can be obtained by deesterification of the corresponding compound of the formula (I) wherein R_1 is an ester group CO_2W. Usually the ester group CO_2R_7 in formula (VIII) will be the same ester group as CO_2W, and for the sake of convenience the ester group CO_2R_6 will normally be the same ester group as CO_2W. The ester group $CO_2W/R_6/R_7$ are suitably C_{1-4} alkyl esters such as methyl ethyl esters.

Generally, the ring closure takes place in a dry organic solvent using a strong base such as sodium hydride or sodium ethoxide (or other $^-OR_6$ or $^-OR_7$ group) to bring about the initial proton abstraction from the α-methylene group. It has been found that sodium ethoxide in benzene, or potassium *t*-butoxide in toluene, benzene or hexamethylphosphoramide give good results.

The preparation of the compounds of formula (VIII) is fully described in our copending UK Patent Application No. 09312/78. (Serial No. 1,524,819).

Compounds within the formula (I) have useful pharmacological activity. For example compounds within the formula (I) have anti-gastric secretion activity, cardiovascular activity e.g. anti-hypertensive activity, platelet aggregration inhibition activity, effect the respiratory tract e.g. bronchodilator activity, and have antifertility and smooth muscle activity.

In general it may be said that compounds within the formula (I) have a range

of pharmacological activities similar to those shown by the natural prostaglandins, but that these activities tend to be rather more selective.

The invention therefore also provides a pharmaceutical composition comprising a compound of the formula (I) and a pharmaceutically acceptable carrier.

Clearly the formulation of the said pharmaceutical composition will depend on the nature of the activity shown by the chosen compound of the formula (I), and on other factors such as a preference in a particular area of therapy for a particular mode of administration. In general however the composition may be formulated for administration by any route.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrollidone; filler for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin, hydroxyethyl-cellulose, carbomethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents. The compounds of the formula (I) may also if desired be incorporated in a foodstuff, for example in the form of a biscuit.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound of the formula (I) and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved for injection and filter sterilized before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents can be dissolved in the vehicle. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactent or wetting agent is included in the composition to facilitate uniform distribution of the compound.

When appropriate, the compositions of this invention may be presented as an aerosol, or as a microfine powder for insufflation.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

It has been found that a number of the compounds of the formula (I) are potent inhibitors of gastric secretion, and thus have commercial utility as anti-ulcer agents. In treatment of this nature, the composition containing the formula (I) will preferably be formulated in a manner to allow oral administration. Normally .01 mg/kg to 500 mg/kg per day, most suitably .1 to 100 mg/kg per day, of the compound of the formula (I) in composition form will be administered in such treatment. Examples of such compounds of the formula (I) include those of formulae (II) and (III) as hereinbefore defined.

Also a number of compounds of the formula (I) have particularly useful activity on the respiratory tract, and thus find utility as for example bronchodilators. Normally compositions containing such compounds of the formula (I) will be formulated as an aerosol, or as a microfine powder for insufflation, and the treatment will comprise the administration of from .001 mg/kg to 100 mg/kg per day of the compound in composition form.

Further, a number of compounds of the formula (I) are particularly potent inhibitors of platelet aggregation, and thus compositions containing such compounds are useful *inter alia* for administration to humans and animals to prevent clot formation for example after surgery to prevent postoperative thrombosis; in geriactric

patients to prevent transient cerebral ischemic attacks; and long-term prophylaxis following myocardial infarcts and strokes—and in general in the treatment or prophylaxis of any disorder caused by an over pronounced tendency of blood platelets to aggregate. Such compositions also have applications in the storage of whole blood in blood banks, and whole blood to be used in heart-lung machines, or to be circulated through organs, e.g. heart and kidneys, which have been removed from a cadaver and prior to transplant.

It will of course be realised that the precise dosage used in the treatment of any of the hereinbefore described disorders will depend on the actual compound of the formula (I) used, and also on other factors such as the seriousness of the disorder being treated.

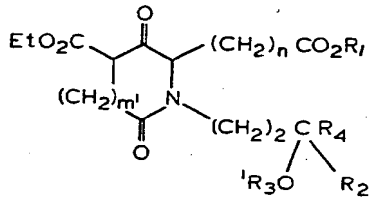
The invention also provides a method of treatment or prophylaxis of disorders in animals other than humans which comprises the administration of an effective amount of a compound of the formula (I).

The following Examples 2 to 16 illustrate the preparation of compounds of the formula (I) and their pharmacological properties.

Example 1 illustrates the preparation of intermediates of formula (VII) from intermediates of formula (VIII).

The preparation of intermediates of formula (VIII) is illustrated in the specific Examples of copending UK Patent Application No. 09312/78 (Serial No. 1,524,819).

EXAMPLE 1.



Method Variant A.

4 - Ethoxycarbonyl - 2 - (6' - ethoxycarbonyl - n - hexyl) - 1 - (3" - hydroxy - 3" - methyl - n - nonyl) - pyrrolidin - 3,5 - diane ($m'=0$; $n=6$; $R_1=C_2H_5$; $R_2=CH_3$; $'R_3=H$; $R_4=n-C_6H_{13}$).

Potassium *tert*-butoxide (5.35 g) was added in small portions over 1 hour to a warm solution of diethyl 2 - [N - (3' - hydroxy - 3' - methyl - *n* - nonyl) - N-ethoxycarbonylacetyl] - aminoazelate (27.5 g) in dry toluene (150 ml). The mixture was gently refluxed for 2 hours.

The solvent was evaporated *in vacuo* and the residue was taken up in water. The solution was extracted twice with diethyl ether and the aqueous layer was acidified with dilute hydrochloric acid and extracted with diethyl ether. This ethereal solution was washed with brine and dried over magnesium sulphate to give a solution of *4 - ethoxycarbonyl - 2 - (6' - ethoxycarbonyl - n - hexyl) - 1 - (3" - hydroxy - 3" - methyl - n - nonyl) - pyrrolidin - 3,5 - dione.*

Method Variant B.

1 - (3 - Benzyloxy - n - octyl) - 4 - ethoxycarbonyl - 2 - (6" - ethoxycarbonyl - n-hexyl) - piperidin - 3,6 - dione ($m'=1$; $n=6$; $R_1=C_2H_5$; $R_2=H$; $'R_3=CH_2Ph$; $R_4=C_5H_{11}$).

Diethyl 2 - [N - (3' - benzyloxy - octyl) - N - (3" - ethoxycarbonyl - propionyl)] - aminoazelate (5 g) was refluxed with potassium *tert*-butoxide (1.05 g) in dry benzene (50 ml) for 4 hours. The benzene was evaporated *in vacuo* and the residue poured into water (100 ml). The aqueous mixture was made just acidic with dilute hydrochloric acid and was extracted with diethyl ether. The ethereal solution was washed with water, dried over magnesium sulphate and evaporated *in vacuo* to give *1 - (3' - benzyloxy - n - octyl) - 4 - ethoxycarbonyl - 2 - (6" - ethoxycarbonyl - n -hexyl) - piperidin - 3,6 - dione* as a yellow gum. (4.5 g).

Method Variant C.

4 - Ethoxycarbonyl - 2 - n - heptyl - 1 - n - octyl - piperidin - 3,6 - dione.

Ethyl 2 - [N - (3' - ethoxycarbonylpropionyl) - N - octyl] - amino - nonanoate (5 g) was added dropwise to a suspension of sodium hydride (0.5 g) in refluxing tetrahydrofuran (200 ml). The mixture was refluxed under nitrogen overnight.

The reaction mixture was concentrated, water was added and the solution acidified with dilute hydrochloric acid. The product was extracted into ether and the ethereal solution was washed, dried over magnesium sulphate and evaporated *in vacuo* to give *4 - ethoxycarbonyl - 2 - n - heptyl - 1 - n - octyl - piperidin - 3,6 - dione* as a yellow oil (4.2 g).

Method Variant D.

Ethoxycarbonyl - 2 - (6' - ethoxycarbonyl - n - hexyl) - 1 - (3'' - benzyloxy - n-nonyl) - pyrrolidin - 3,5 - dione (m'=0; n=6; R_1=C_2H_5; R_2=H; R_3=CH_2Ph; R_4=C_6H_{13}).

A solution of diethyl 2 - [N - (3' - benzyloxy - *n* - nonyl) - N - ethoxy - carbonylacetyl] - aminoazelate (0.5 g) in hexamethylphosphoramide (5 ml) was added to a solution of potassium *tert*-butoxide (0.11 g) in hexamethylphosphoramide (5 ml). The mixture was stirred at room temperature for 1 hour.

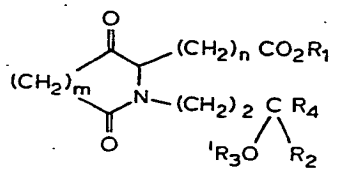
The reaction mixture was poured into dilute hydrochloric acid and extracted with ether. The ether extracts were washed with brine and dried over anhydrous sodium sulphate to give a solution of *4 - ethoxycarbonyl - 2 - (6' - ethoxycarbonyl - n - hexyl)-1 - (3'' - benzyloxy - n - nonyl) - pyrrolidin - 3,5 - dione.*

The products shown in Table 1 were similarly prepared.

TABLE 1

Compound	m'	n	R_1	R_2	R_3	R_4	Method Variant
35	1	6	C_2H_5	H	Ch_2Ph	*n*-C_6H_{13}	B
36	0	6	C_2H_5	H	Ch_2Ph	*n*-C_5H_{11}	B
37	0	6	C_2H_5	H	Ch_2Ph	H	B
38	1	6	C_2H_5	CH_3	H	*n*-C_5H_{11}	B
39	1	6	C_2H_5	CH_3	H	*n*-C_6H_{13}	A
40	1	6	C_2H_5	CH_3	H	*n*-C_7H_{15}	A
41	1	6	C_2H_5	CH_3	H	*n*-C_8H_{17}	A
42	1	7	C_2H_5	CH_3	H	*n*-C_6H_{13}	A
43	1	6	C_2H_5	CH_3	H	$CH(CH_3)(CH_2)_4CH_3$	A
44	0	6	C_2H_5	CH_3	H	*n*-C_4H_9	A
45	0	6	C_2H_5	CH_3	H	*n*-C_5H_{11}	A
46	0	6	C_2H_5	CH_3	H	*n*-C_7H_{15}	A
47	0	6	C_2H_5	CH_3	H	*n*-C_8H_{17}	A
48	0	7	C_2H_5	CH_3	H	*n*-C_6H_{13}	A
49	0	5	C_2H_5	CH_3	H	*n*-C_6H_{13}	A
50	0	6	C_2H_5	C_2H_5	H	*n*-C_6H_{13}	A
51	0	6	CH_3	CH_3	H	*n*-C_6H_{13}	A

EXAMPLE 2.



Method Variant A.

2 - (6' - Ethoxycarbonyl - n - hexyl) - 1 - (3'' - hydroxy - 3'' - methyl - n - nonyl) - pyrrolidin - 3,5 - dione (m=1; n=6; R_1=C_2H_5; R_2=CH_3; 'R$_3$=H; R_4=C_6H_{13}).

A solution of 4 - ethoxycarbonyl - 2 - (6' - ethoxycarbonyl - n - hexyl) - 1-(3'' - hydroxy - 3'' - methyl - n - nonyl) - pyrrolidin - 3,5 - dione in diethyl ether was allowed to stand over magnesium sulphate at room temperature overnight. The solution was filtered and the filtrate evaporated *in vacuo* to give *2 - (6' - ethoxycarbonyl - n - hexyl) - 1 - (3'' - hydroxy - 3'' - methyl - n - nonyl) - pyrrolidin - 3,5-dione* as a yellow oil.

Method Variant B.

1 - (3' - Benzyloxy - n - octyl) - 2 - (6'' - ethoxycarbonyl - n - hexyl) - piperidin-3,6 - dione (m=2; n=6; R_1=C_2H_5; R_2=H; 'R$_3$=CH_2Ph; R_4=C_5H_{11}).

1 - (3' - Benzyloxy - n - octyl) - 4 - ethoxycarbonyl - 2 - (6'' - ethoxy - carbonyl - n - hexyl) - piperidin - 3,6 - dione (8.3 g) was refluxed with lithium iodide dihydrate (4 g) in dry dimethylformamide (70 ml) for 3 hours. The solvent was evaporated *in vacuo* and the residue treated with very dilute hydrochloric acid. The product was extracted into diethyl ether and the ethereal solution was washed with water, dried over magnesium sulphate and evaporated *in vacuo* to give a pale yellow oil. The product was purified by column chromatography to give *1 - (3' - benzyloxy-n - octyl) - 2 - (6'' - ethoxy - carbonyl - n - hexyl) - piperidin - 3,6 - dione* as a pale yellow gum (2.0 g, 28% yield).

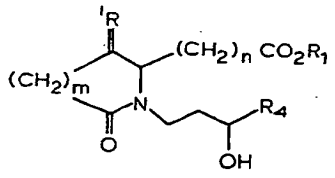
Method Variant C.

1 - (3' - Benzyloxy - n - octyl) - 2 - (6'' - ethoxycarbonyl - n - hexyl) - pyrrolidin - 3,5 - dione (m=1; n=6; R_1=C_2H_5; R_2=H; 'R$_3$=CH_2Ph; R_4=C_5H_{11}.

A solution of 1 - (3' - benzyloxy - n - octyl) - 4 - ethoxycarbonyl - 2 - (6''-ethoxycarbonyl - n - hexyl) - pyrrolidin - 3,5 - dione (5.4 g) in dry xylene was refluxed for 2 hours. The solvent was evaporated *in vacuo* and the product purified by gel filtration to give *1 - (3' - benzyloxy - n - octyl) - 2 - (6'' ethoxycarbonyl-n - hexyl) - pyrrolidin - 3,5 - dione* as a yellow gum (2.0 g, 43% yield).

The products shown in Table 2 were similarly prepared.

EXAMPLE 3.



2 - (6' - Ethoxycarbonyl - n - hexyl) - 1 - (3'' - hydroxy - n - octyl) - piperidin - 3,6-dione (m=2; n=6; 'R=0; R_1=C_2H_5; R_4=C_5H_{11}).

10% Palladium on charcoal (1.4 g) was added to a solution of 1 - (3' - benzyloxy - n - octyl) - 2 - (6'' - ethoxycarbonyl - n - hexyl) - piperidin - 3,6 - dione (2.8 g) in dry 1,2-dimethoxyethane (25 ml) and the mixture was hydrogenated at room temperature and atmospheric pressure for 1 hour. The reaction mixture was filtered through kieselguhr and the filtrate evaporated *in vacuo* to give *2 - (6'-ethoxycarbonyl - n - hexyl) - 1 - (3'' - hydroxy - n - octyl) - piperidin - 3,6-dione* (2.05 g) as a yellow gum.

The products shown in Table 3 were similarly prepared.

TABLE 2

Compound	m	n	R_1	R_2	R_3	R_4	Method Variant
52	2	6	C_2H_5	H	CH_2Ph	n-C_6H_{13}	B
53	1	6	C_2H_5	H	CH_2Ph	n-C_6H_{13}	C
54	1	6	C_2H_5	H	CH_2Ph	H	C
55	2	6	C_2H_5	CH_3	H	n-C_5H_{11}	B
56	2	6	C_2H_5	CH_3	H	n-C_6H_{13}	B
57	2	6	C_2H_5	CH_3	H	n-C_7H_{15}	B
58	2	6	C_2H_5	CH_3	H	n-C_8H_{17}	B
59	2	7	C_2H_5	CH_3	H	n-C_6H_{13}	B
60	2	6	C_2H_5	CH_3	H	$CH(CH_3)(CH_2)_4CH_3$	B
61	1	6	C_2H_5	CH_3	H	n-C_4H_9	A
62	1	6	C_2H_5	CH_3	H	n-C_5H_{11}	A
63	1	6	C_2H_5	CH_3	H	n-C_6H_{13}	A
64	1	6	C_2H_5	CH_3	H	n-C_7H_{15}	A
65	1	6	C_2H_5	CH_3	H	n-C_8H_{17}	A
66	1	7	C_2H_5	CH_3	H	n-C_6H_{13}	A
67	1	5	C_2H_5	CH_3	H	n-C_6H_{13}	A
68	1	6	C_2H_5	C_2H_5	H	n-C_6H_{13}	A
69	1	6	CH_3	CH_3	H	n-C_6H_{13}	A
70	1	6	n-C_4H_9	CH_3	H	n-C_6H_{13}	A
71	1	6	t-C_4H_9	CH_3	H	n-C_6H_{13}	A

2 - n - Heptyl - 1 - n - octyl - piperidin - 3,6 - dione was similarly prepared using Method Variant C.

TABLE 3

Compound	m	n	'R	R_1	R_4
72	2	6	H,OH	C_2H_5	H
73	2	6	O	C_2H_5	n-C_5H_{11}
74	2	6	O	C_2H_5	H
75	1	6	O	C_2H_5	n-C_5H_{11}
76	1	6	H,OH	C_2H_5	n-C_5H_{11}
77	1	6	O	C_2H_5	n-C_6H_{13}
78	2	6	O	C_2H_5	n-C_6H_{13}

EXAMPLE 4.

2 - (6' - Ethoxycarbonyl - n - hexyl) - 3 - hydroxy - 1 - (3" - hydroxy - n - octyl)-pyrrolidin - 5-one.

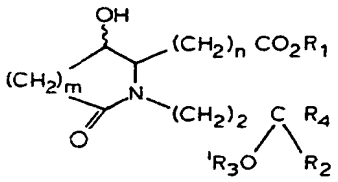
Sodium borohydride (100 mg) was added in portions to a stirred solution of 2 - (6' - ethoxycarbonyl - n - hexyl) - 1 - (3" - hydroxy - n - octyl) - pyrrolidin-3,5 - dione (870 mg) in dry ethanol (10 ml). Stirring was continued for 2 hours at room temperature.

The solvent was evaporated *in vacuo* and the residue was dissolved in diethyl ether. The ethereal solution was washed with very little dilute hydrochloric acid and with water, dried over magnesium sulphate and evaporated *in vacuo* to give a yellow gum.

The product was purified by chromatography to give *2 - (6' - ethoxycarbonyl-n - hexyl) - 3 - hydroxy - 1 - (3" - hydroxy - n - octyl) - pyrrolidin - 5 - one* as a colourless gum (410 mg, 47% yield).

The products shown in Table 4 were similarly prepared:

TABLE 4



Compound	m	n	R_1	R_2	$^1R_3$	R_4
79	2	6	C_2H_5	H	CH_2Ph	n-C_5H_{11}
80	2	6	C_2H_5	H	CH_2Ph	H
81	1	6	C_2H_5	H	CH_2Ph	n-C_5H_{11}
82	1	6	C_2H_5	H	CH_2Ph	H
83	1	6	C_2H_5	H	CH_2Ph	n-C_6H_{13}
84	1	6	C_2H_5	CH_3	H	n-C_5H_{11}
85	2	6	C_2H_5	CH_3	H	n-C_6H_{13}
86	1	6	C_2H_5	CH_3	H	n-C_6H_{13}
87	2	6	C_2H_5	CH_3	H	$CH(CH_3)(CH_2)_4CH_3$
88	2	6	C_2H_5	CH_3	H	n-C_7H_{15}
89	1	6	C_2H_5	CH_3	H	n-C_7H_{15}
90	2	6	C_2H_5	CH_3	H	n-C_8H_{17}
91	1	6	C_2H_5	C_2H_5	H	n-C_6H_{13}
92	1	6	C_2H_5	CH_3	H	n-C_4H_9
93	1	7	C_2H_5	CH_3	H	n-C_6H_{13}
94	1	5	C_2H_5	CH_3	H	n-C_6H_{13}
95	1	6	C_2H_5	CH_3	H	n-C_8H_{17}
96	2	6	C_2H_5	H	H	n-C_5H_{11}
97	2	6	C_2H_5	H	H	n-C_6H_{13}
98	1	6	C_2H_5	H	H	n-C_6H_{13}

Compound 99, *2 - n - Heptyl - 3 - hydroxy - 1 - n - octyl - piperidin - 6-one,* and *2 - (6' - ethoxycarbonyl - n - hexyl) - 3 - hydroxy - 1 - n - octyl - piperidin-6 - one* were also prepared similarly.

EXAMPLE 5.

2 - (6' - Carboxy - n - hexyl) - 3 - hydroxy - 1 - (3" - hydroxy - 3" - methyl - n-decyl) - pyrrolidin - 5 - one.

A 10% w/v solution of potassium carbonate (20 ml) was added to a solution of 2 - (6' - ethoxycarbonyl - n - hexyl) - 3 - hydroxy - 1 - (3" - hydroxy - 3" - methyl-n - decyl) - pyrrolidin - 5 one (2 g) in ethanol (20 ml). This mixture was gently refluxed for 2 hours.

The solvent was evaporated *in vacuo* and the residue was taken up in water. The aqueous solution was extracted with diethyl ether and acidified with dilute hydrochloric acid. The acid solution was extracted with diethyl ether and this ethereal solution was washed with water, dried over magnesium sulphate and evaporated *in vacuo* to give a colourless oil. The product was purified by chromatography to give *2 (6' - carboxy - n - hexyl) - 3 - hydroxy - 1 - (3" - hydroxy - 3" - methyl - n-decyl) - pyrrolidin-5-one* as a colourless oil 900 mg, 48% yield).

EXAMPLE 6.

2 - (6' - Carboxy - n - hexyl) - 1 - (3" - hydroxy - n - nonyl) - pyrrolidin - 3,5 dione.

A solution of 2 - (6' - ethoxycarbonyl - n - hexyl) - 1 - (3" - hydroxy - n-nonyl) - pyrrolidin - 3,5 - dione (2 g) in ethanol (25 ml) was added dropwise to a solution of 10% w/v sodium hydroxide (25 ml) in ethanol (25 ml). The mixture was refluxed for 3 hours.

The solvent was evaporated *in vacuo* and the residue was dissolved in water. The aqueous solution was extracted with diethyl ether, acidified and the acid solution extracted twice with diethyl ether. These ethereal extracts were combined, washed with saturated brine, dried over magnesium sulphate and evaporated *in vacuo* to give *2 - (6' - carboxy - n - hexyl) - 1 - (3" - hydroxy - n - nonyl) - pyrrolidin - 3,5-dione* as a colourless oil (1.5 g, 80% yield).

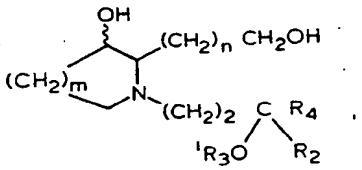
EXAMPLE 7.

1 - (3' - Benzyloxy - n - octyl) - 3 - hydroxy - 2 - (7" - hydroxy - n - heptyl)-piperidine.

1 - (3' - Benzyloxy - n - octyl) - 2 - (6" - ethoxycarbonyl - n - hexyl) - piperidin - 3,6 - dione (1 g) was stirred, under reflux, with lithium aluminium hydride (156 mg) in dry diethyl ether (30 ml) for 4 hours. The mixture was cooled in an ice-bath and water (1.5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 30 minutes and filtered. The residue was washed several times with diethyl ether and the combined ethereal solutions were dried over magnesium sulphate and evaporated *in vacuo* to give *1 - (3' - benzyloxy - n - octyl) - 3-hydroxy 2 - (7" - hydroxy - n - heptyl) - piperidine* as a yellow oil (730 mg, 82% yield).

The products shown in Table 5 were similarly prepared.

TABLE 5



Compound	m	n	R_2	$'R_3$	R_4
100	2	6	H	H	n-C_5H_{11}
101	1	6	H	CH_2Ph	n-C_5H_{11}
102	1	6	H	H	n-C_5H_{11}
103	2	6	H	CH_2Ph	H
104	2	6	H	CH_2Ph	n-C_5H_{11}
105 (a)	2	6	H	H	n-C_6H_{13}
106	1	6	H	CH_2Ph	H
107 (a)	1	6	H	CH_2Ph	n-C_6H_{13}
108 (a)	1	6	H	H	n-C_6H_{13}
109 (a)	2	6	CH_3	H	n-C_6H_{13}
110 (a)	1	6	CH_3	H	n-C_7H_{15}
111 (a)	2	6	CH_3	H	n-C_8H_{17}

(a) Product purified by chromatography

Compound 112, *2 - n - heptyl - 3 - hydroxy - 1 - n - octyl - piperidine* was also prepared similarly.

EXAMPLE 8.

2 - (6' - Ethoxycarbonyl - n - hexyl) - 1 - (3" - oxo - n - octyl) - piperidin - 3,6-dione.

Jones' reagent was added dropwise to a solution of 2 - (6' - ethoxycarbonyl - n-hexyl) - 1 - (3" - hydroxy - n - octyl) - piperidine - 3,6 - dione (500 mg) in acetone (10 ml) at 0° until the yellow colour persisted. The stirred solution was allowed to warm to room temperature and diethyl ether (50 ml) and water (50 ml) were added. The organic phase was separated, washed with water, dried over magnesium sulphate and evaporated *in vacuo* to give 2 - (6' - ethoxycarbonyl - n - hexyl) - 1 - (3"-*oxo - n - octyl) - piperidine - 3,6- - dione* as a yellow gum (500 mg, quantitive yield).

EXAMPLE 9.

3 - Benzyloxy - 2 - n - heptyl - 1 - n - octyl - piperidine.

A solution of 2 - n - heptyl - 3 - hydroxy - 1 - n - octyl - piperidine (2.8 g) in dry dioxan (20 ml) was added dropwise to a stirred suspension of sodium hydride (216 mg) in dry dioxan (5 ml) and the mixture was refluxed for 1 hour. Benzyl bromide (1.54 g) in dry dioxan (5 ml) was added dropwise to the cooled solution and the mixture was refluxed overnight.

The solvent was evaporated *in vacuo* and the residue was partitioned between diethyl ether and water. The ethereal phase was washed with water, dried over magnesium sulphate and evaporated *in vacuo*. The product was purified by column chromatography to give *3 - benzyloxy - 2 - n - heptyl - 1 - n - octyl - piperidine* as a yellow oil (1.3 g, 36% yield).

EXAMPLE 10.

2 - n - Heptyl 1 n - octyl - piperidin - 3 - one.

Jones' reagent (116.1 ml) was added dropwise to a stirred solution of 2 - n-heptyl - 3 - hydroxy - 1 - n - octyl - piperidine (16.6 g) in actone (160 ml) at room temperature. The reaction mixture was stirred for 6 hours and filtered through kieselguhr. The residue was washed several times with diethyl ether and the combined organic solutions were extracted with 5% w/v sodium hydroxide solution. The aqueous phase was washed with ether and the combined organic phases were washed with water, dried over magnesium sulphate and evaporated *in vacuo*. The product was purified by chromatography to give *2 - n - heptyl - 1 - n - octyl - piperidin - 3-one* as a yellow gum (5.71 g, 34% yield).

EXAMPLE 11.

2 - n - Heptyl - 3 - hydroxy - 3 - methyl - 1 - n - octyl - piperidine.

Methyl lithium (7 ml, 2M solution in diethyl ether) was injected, under nitrogen, into a stirred solution of 2 - n - heptyl - 1 - n - octyl - piperidine - 3 - one (3.4 g) in dry diethyl ether (100 ml) at −78°. The mixture was allowed to warm gradually to room temperature. After 3 hours, thin layer chromatography indicated that some starting material remained. The solution was cooled to −78° and methyl lithium (3 ml, 2M solution in diethyl ether) was injected. The mixture was allowed to warm gradually to room temperature and was allowed to stand for 2 days. Water (10 ml) was added dropwise and the ethereal phase was separated, dried over magnesium sulphate and evaporated *in vacuo*. The product was purified by column chromatography to give *2 - n - heptyl - 3 - hydroxy - 3 - methyl - 1 - n - octyl - piperidine* as a yellow gum (1.47 g, 41% yield).

EXAMPLE 12.

2 - n - Heptyl - 3 - hydroxy - 1 - n - octyl - piperidine hydrogen tartrate.

2 - n - Heptyl - 3 - hydroxy - 1 - n - octyl - piperidine (500 mg) and D-tartaric acid (241 mg) were mixed together in acetone. The solvent was evaporated *in vacuo* to give *2 - n - heptyl - 3 - hydroxy - 1 - n - octyl - piperidine hydrogen tartrate* as a yellow gum (740 mg, quantitive yield).

EXAMPLE 13.

3 - Acetoxy - 2 - (7' - acetoxy - n - heptyl) - 1 - (3" - benzyloxy) - n - octyl)-piperidine.

1 - (3' - Benzyloxy - n - octyl) - 3 - hydroxy - 2 - (7" - hydroxy - n - heptyl)-piperidine (2 g in dry benzene (30 ml) was treated with acetic anhydride (1.2 ml). The mixture was stirred overnight at room temperature.

The solvent was evaporated *in vacuo* and the residue was dissolved in diethyl ether (300 ml). The ethereal solution was washed with concentrated sodium hydroxide solution and with brine, dried over magnesium sulphate and evaporated *in vacuo*. The product was purified by column chromatography to give *3 - acetoxy - 2 - (7'-acetoxy - n - heptyl) - 1 - (3" - benzyloxy - n - octyl) - piperidine* as a yellow oil (1.05 g, 43% yield).

EXAMPLE 14.

3,3 - Ethylenedioxy - 2 - n - heptyl - 1 - n - octyl - piperidin - 6 - one.

Ethylene glycol (1.2 g) and toluene - *p* - sulphonic acid (30 mg) were added to a solution of 2 - n - heptyl - 1 - n - octyl - piperidin - 3,6 - dione (0.6 g) in dry toluene (25 ml) and the mixture was refluxed under a Dean and Stark head for 3 hours.

The reaction mixture was diluted with water and extracted with diethyl ether. The ethereal solution was washed with sodium carbonate solution and with water, dried over magnesium sulphate and evaporated *in vacuo* to give *3,3 - ethylenedioxy-2 - n - heptyl - 1 - n - octyl - piperidin - 6 - one* as a yellow oil (576 mg. 85% yield).

EXAMPLE 15.

2 - (6' - Ethoxycarbonyl - n - hexyl) - 1 - (3" - hydroxy - 3" - methyl - n - decyl)-piperidin - 6 - one - 3 - semicarbazone.

2 - (6' - Ethoxycarbonyl - n - hexyl) - 1 - (3" - hydroxy - 3" - methyl - n-decyl) - piperidin - 3,6 - dione (750 mg) was added to a solution of semicarbazide hydrochloride (1 g) and sodium acetate (1.5 g) in water (10 ml). Ethanol was added until a clear solution was obtained and the mixture was shaken for 1 hour.

The reaction mixture was extracted with diethyl ether and the ethereal solution was washed with brine, dried over magnesium sulphate and evaporated *in vacuo*. The product was purified by preparative layer chromatography and crystallised from ether to give *2 - (6' - ethoxycarbonyl - n - hexyl) - 1 - (3'' - hydroxy - 3'' - methyl-n - decyl) - piperidin - 6 - one - 3 - semicarbazone* as a white solid (260 mg, 31% yield), m.p. 88°.

EXAMPLE 16.

PHARMACOLOGICAL DATA.

The compounds were tested for prostaglandin-like and for prostagandin antagonist activity in a number of pharmacological tests.

1. *Anti-secretory/anti-ulcer activity.*

a. The compounds were examined for their ability to inhibit pentagastrin-stimulated gastric acid secretion in the anaesthetised, perfused rat stomach preparation (Ghosh and Schild preparation).

M. N. Ghosh and H. O. Schild, (1958), Brit. J. Pharmacol, *13*, 54.

The compounds were given intravenously. Some of the results are shown in Table 6.

TABLE 6

Compound Number	Active dose range mg/kg	ED_{50} mg/kg
56	0.5 → 20	–
60	0.5 → 5	1.0
62	0.1 → 5	0.72
63	0.05 → 0.5	0.09
77	1 → 10	2.6
78	1 → 10	–

b. The compounds were examined for their ability to inhibit gastric acid secretion in the pyloric ligated rat model (Shay rat preparation).

H. Shay, S. A. Komarov, S. S. Fels, D. Merance, M. Gruenstein and H. Siplet, (1945), Gastroenterology, *5*, 43.

When given subcutaneously twice in a 3 hour Shay rat preparation, once at the time of ligation and again 1.5 hours after ligation, Compound 63 lowered the total titratable acidity in the stomach by inhibiting the volume of secretion and by decreasing the H^+ concentration. The ED_{50} was 2.25 mg/kg × 2, s.c.

When given subcutaneously once in a 3 hour Shay rat preparation at the time of ligation, Compound 63 had an ED_{50} of 5.3 mg/kg, s.c. Similarly, Compound 63 was active when given intraduodenally in the Shay rat preparation.

c. The compounds were examined for their ability to inhibit gastric acid secretion, stimulated by pentagastrin infusion, in the chronic fistula rat preparation.

P. H. Guth and R. Mendick, (1965), Amer. J. Gastroenterology, *44*, 545.

Compound 63 when given subcutaneously was very effective in inhibiting acid secretion at 2—5 mg/kg, s.c.

d. Anti-ulcer activity was determined in a 5 hour indomethacin-induced (50 mg/kg, i.p.) ulcer test in fasted rats. Compound 63 inhibited ulceration by 71% when given at 20 mg/kg, s.c., twice during the course of the test.

2. *Respiratory system.*

Bronchodilator activity.

a. The compounds were examined for their ability to inhibit 5 - hydroxy - tryptamine - induced bronchoconstriction in the anaesthetised, artificially respired guinea pig (Konsett- Rossler preparation).

H. Konsett and R. Rossler, (1940), Naunyn-Schneidebergs Arch. Exp. Path. Pharmak., *195*, 71.

After preparation of the guinea pig, a dose of 5 - hydroxy - tryptamine producing an adequate response was determined by dosing, i.v., every 6 minutes. This dose was usually 10 μg. After a standard response was obtained, compounds were given intravenously 2 minutes prior to the next standard dose and dosing of 5 - hydroxytryptamine was continued every 6 minutes until the response returned to control values. Some of the results are shown in Table 7.

TABLE 7

Compound Number	ED_{50} μg/kg
57	253
62	88
63	8
64	11
77	380
86	505

b. The compounds were examined for their ability to protect against aerosol administered, histamine-induced asphyxic collapse in guinea pigs.

M. A. Wasserman and R. L. Griffen, (1975), Am. Rev. Resp. Dis., *111*, 946.

Many of the compounds, such as Compounds 63 and 64, were very effective in protecting against histamine challenge.

3. *Cardiovascular activity.*

a. The effect of the compounds on arterial blood pressure was determined in the anaesthetised, normotensive rat. The rat preparation was similar to that described in "Pharmacological experiments on intact preparations", E. and S. Livingstone, Edinburgh and London, 1970, p. 63.

The compounds were administered intra-venously and some of the results are shown in Table 8. The active compounds were predominantly depressor agents in the normotensive rat.

TABLE 8

Compound Number	Dose range mg/kg	% Depression at 1 mg/kg
62	0.001 → 1.0	70
63	0.001 → 1.0	60
77	0.01 → 1.0	30
78	0.01 → 1.0	30
105	0.01 → 1.0	20

b. The vasodilator activity of the compounds was determined in the femoral artery of the hind limb of the anaesthetised beagle dog. The method used was similar to that described by J. Nakano and J. R. McCurdy, (1967), J. Pharmac. Exp. Ther., *156*, 538.

The compounds were administered into the iliac artery and the effects on both flow and pressure in the hind limb were recorded. Changes in vascular resistance (R) were calculated from the following expression:

$$R = \frac{\text{mean arterial pressure}}{\text{mean flow}}$$

Some of the compounds, for example Compounds 63, 73 and 112, decreased vascular resistance over a dose range of 0.01—1 mg/kg, when given intra-arterially.

In other experiments the compounds were administered into the left femoral vein and the right femoral arterial pressure and cardiac output were monitored. From these experiments, total peripheral resistance (TPR) was calculated from the expression:

$$TPR = \frac{\text{mean arterial pressure}}{\text{cardiac output}}$$

Some of the compounds, such as Compounds 63, 73 and 112, decreased total peripheral resistance over a dose range of 0.01—10 mg/kg, when given intra-venously.

c. The anti-hypertensive activity of the compounds was determined in the renal hypertensive rat. Rats were made hypertensive by nephrectomy and treatment with deoxycorticosterone acetate/NaCl. The compounds were administered orally to a group of 3 hypertensive rats at a dose level of 100 mg/kg and their blood pressure was monitored after 4, 6 and 24 hours.

Compound 73 gave a 16% fall in blood pressure after 4 hours. The blood pressure had risen to normal hypertensive levels after 6 hours.

4. *Inhibition of platelet aggregration.*

a. The compounds were examined for their ability to inhibit guinea pig platelet aggregation induced, *in vitro*, by 5.45×10^{-7} M adenosine diphosphate (ADP).

The method consisted of diluting the compound immediately before use from a 10 mg/ml solution in ethanol to a 1 mg/ml solution with saline and then adding the appropriate volume to 0.5 ml of plateful rich plasma. The mixture was stirred at 37° C for 1 minute before 25 μl of an ADP solution was added to give a final ADP concentration of 5.45×10^{-7} M. The aggregration response was then recorded relative to the control.

Some of the results are shown in Table 9.

TABLE 9

Compound Number	IC_{50} μM
56	51
60	11
62	20
63	1.3
64	9.0
68	4.0
73	44
76	147
77	5.4
86	55

b. The compounds were examined for their ability to inhibit human platelet aggregation induced, *in vitro*, either by adenosine diphosphate (ADP) or collagen. The compounds were added in saline or dimethylformamide to platelet rich plasma at 37° C to give a final concentration of 10^{-4} M. After 3 minutes the platelets were challenged with ADP or collagen. The aggregration response was then recorded relative to the control. Some of the results are shown in Table 10. Only compounds giving a greater than 50% inhibition at 10^{-4} M were regarded as active.

TABLE 10

Compound Number	% Inhibition at 10^{-4}M	
	ADP	Collagen
73	87	100
75	—	61
76	—	79
78	—	65
102	—	71
105	—	78
112	—	77

The IC_{50} for Compound 73 against collagen-induced aggregration was 2.8 μM.

5. *Smooth muscle activity.*

a. *Gerbil colon in vitro.*

The compounds were tested for prostaglandin-like and for prostaglandin

antagonist activity on the isolated perfused gerbil colon preparation (smooth muscle). This has been shown by J. R. Weeks, J. R. Schultz and W. E. Brown, (1968), J. App. Physiol, *25*, 783, to have greater precision and sensitivity than other preparations. A 15 mm portion of the descending colon is suspended in an organ bath and perfused with De Jalon's saline at 32° C. Compounds were given in a three minute cycle with a 45 second contact time and a 15 second washout time. Antagonist compounds were given with a one minute pre-contact time.

Prostaglandin-like activity was determined using the method of H. O. Schild, (1942), J. Physiol., *101*, 115, which is a standard 4 × 4 latin square assay. Some of the compounds stimulated the gerbil colon to contract which is a prostaglandin-like effect, and the results are shown in Table 11.

TABLE 11

Compound number	Concentration/ml. for contractions (μg/ml)
74	4 – 8
75	0.2 – 0.5
100	0.01 – 0.02
101	0.04 – 0.10
102	0.04 – 0.10

Antagonist activity was determined by measuring the percentage reduction of the contraction to two standard doses of prostaglandin $F_{2\alpha}$ which gave responses between 20% and 80% of maximum response. From this data the IC_{50} values were calculated and the results for some of the compounds are shown in Table 12.

TABLE 12

Compound number	IC_{50} μg/ml
73	3.4
79	0.76
80	3.1
81	0.17
98	2.15
99	1.55
103	0.35
104	0.11

b. *Rat stomach strip in vitro.*

Some of the compounds were tested for prostaglandin-like activity on the isolated rat stomach strip preparation. Some of the compounds weakly stimulated the isolated tissue.

6. *Antifertility activity.*

Antifertility activity was determined by subcutaneous dosing of female mice for 5 days pre-coitally and 10 days post-coitally. Three female mice per group were used and these were mated with males of proven fertility and mating confirmed by examination for copulation plugs.

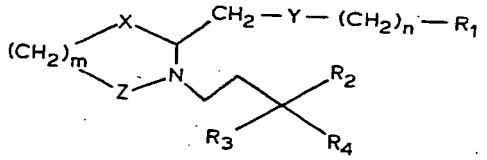
Some of the compounds, such as Compounds 108 and 112, were active at 50—100 mg/kg, s.c.

The pharmacological and therapeutic values of compounds with prostaglandin-like activity, for example, as anti-hypertensive agents, as fertility control agents, as inhibitors of gastric secretion and as bronchodilators is well known. S. Bergstrom, L. A. Carlson and J. R. Weeks, (1968), Pharma. Rev., *20*, 1; F. Cassidy, (1971), Rep. Prog. Appl. Chem., *56*, 695; The Prostaglandins, Progress in Research, S. M. M. Karim, Medical and Technical Publishing Co. Ltd., Oxford and Lancaster, 1972.

Compounds which antagonise the action of prostaglandins are of pharmacological significance. Such prostaglandin antagonists are of potential value in the control of gastro-intestinal hypermotility, in the prevention of premature labour and in the control of inflammation. (see The Prostaglandins, loc. cit.).

WHAT WE CLAIM IS:—

1. A compound of the formula (I):



(I)

wherein:

X is CO, protected CO, CROH in which R is hydrogen or C_{1-4} alkyl and in which the OH moiety may be protected;

Y is CH_2CH_2 or *cis*- or *trans*-$CH=CH$;

Z is CO or CH_2;

n is 1 to 8;

m is 1, 2 or 3;

R_1 is hydrogen, CH_2OH, CH_2OH in which the OH moiety is protected, CO_2W wherein W is hydrogen or CO_2W represents an ester group in which the ester moiety contains from 1 to 12 carbon atoms, or $CONH_2$;

R_2 is hydrogen, C_{1-4} alkyl, or taken together with R_3 and the carbon atom to which it is attached represents a carbonyl group;

R_3 is hydrogen, hydroxy or protected hydroxy;

R_4 is hydrogen, or C_{1-9} alkyl;

and salts thereof.

2. A compound according to claim 1, wherein Z is CO.

3. A compound according to claim 1 or claim 2, wherein X is CO.

4. A compound according to any one of the claims 1 to 3, wherein Y is CH_2CH_2.

5. A compound according to any one of the claims 1 to 4, wherein n is 3, 4 or 5.

6. A compound according to claim 5, wherein n is 3.

7. A compound according to any one of the claims 1 to 6, wherein m is 1 or 2.

8. A compound according to claim 7, wherein m is 1.

9. A compound according to any one of the claims 1 to 8, wherein R_1 is CO_2W.

10. A compound according to claim 9, wherein W is hydrogen or C_{1-4} alkyl.

11. A compound according to any one of the claims 1 to 10, wherein R_2 is hydrogen or C_{1-4} alkyl.

12. A compound according to any one of the claims 1 to 11, wherein R_3 is hydroxy.

13. A compound according to any one of the claims 1 to 12, wherein R_4 is C_{4-9} alkyl.

14. A compound according to claim 1, wherein X is CHOH Z is CH_2 and R_1 is CH_2OH.

15. A compound according to claim 1, wherein X is CO, CROH in which R is hydrogen or C_{1-4} alkyl and in which the OH moiety may be protected, n is 3 to 8, and R_2 is hydrogen or methyl, or taken together with R_3 and the carbon atom to which it is attached represents a carbonyl group.

16. A compound according to claim 15, wherein Z is CO.

17. A compound according to claim 15 or 16, wherein X is CO.

18. A compound according to any one of the claims 15 to 17, wherein Y is CH_2CH_2.

19. A compound according to any one of the claims 15 to 18, wherein n is 3, 4 or 5.

20. A compound according to claim 19, wherein n is 3.

21. A compound according to any one of the claims 15 to 20, wherein m is 1 or 2.

22. A compound according to claim 21, wherein m is 1.

23. A compound according to any one of the claims 15 to 22, wherein R_1 is CO_2W.

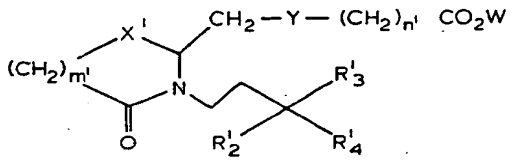
24. A compound according to claim 23, wherein W is hydrogen or C_{1-4} alkyl.

25. A compound according to any one of the claims 15 to 24, wherein R_3 is hydroxy.

26. A compound according to any one of the claims 15 to 25, wherein R_4 is C_{4-9} alkyl.

27. A compound according to claim 15, wherein X is CHOH, Z is CH_2 and R_1 is CH_2OH.

28. A compound of the formula (II):



(II)

wherein:
X^1 is CO, or CHOH or $C(CH_3)OH$ in which the OH group may be protected;
Y is CH_2CH_2 or *cis*- or *trans*-CH=CH;
m^1 is 1 or 2;
n^1 is 1 to 5;
R^1_2 is hydrogen or C_{1-4} alkyl;
R^1_3 is hydrogen, hydroxy or protected hydroxy;
R^1_4 is hydrogen or C_{4-9} alkyl;
W is hydrogen or CO_2W represents an ester group in which the ester moiety contains from 1 to 12 carbon atoms; and salts thereof.

29. A compound according to claim 28, wherein n^1 is 3 to 5 and R^1_2 is hydrogen or methyl.

30. A compound according to claim 29, wherein n^1 is 3.

31. A compound according to claim 29 or 30, wherein X^1 is CO.

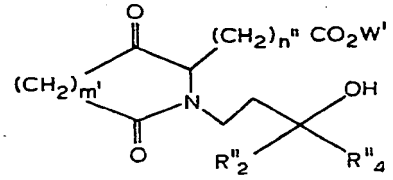
32. A compound according to any one of claims 29 to 31, wherein R^1_3 is hydroxy.

33. A compound according to any one of the claims 29 to 32, wherein R^1_4 is *n*-butyl, *n*-pentyl, *n*-hexyl or *n*-heptyl, or such a group branched by one or two methyl groups at the same or different carbon atoms.

34. A compound according to claim 33, wherein R^1_4 is *n*-pentyl, *n*-hexyl or *n*-heptyl.

35. A compound according to any one of the claims 29 to 34, wherein W is hydrogen or C_{1-4} alkyl.

36. A compound of the formula (III):



(III)

wherein:
m^1 is 1 or 2;
n^{11} is 6:
R^{11}_2 is hydrogen, methyl or ethyl;
R^{11}_4 is *n*-pentyl, *n*-hexyl or *n*-heptyl; and
W^1 is hydrogen or C_{1-4} alkyl; and salts thereof.

37. A compound according to claim 36, wherein R^{11}_2 is methyl.

38. A compound according to claim 37, wherein m^1 is 1.

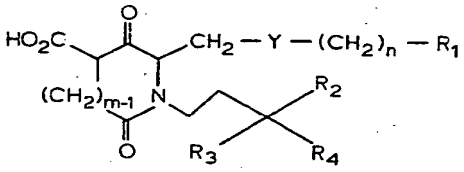
39. A compound according to claim 37 or 38, wherein R^{11}_4 is *n*-hexyl.

40. A compound according to claim 37, 38, or 39 wherein W^1 is ethyl.

41. The compound:
2 - (6′ - Ethoxycarbonyl - *n* - hexyl) - 1 - (3″ - hydroxy - 3″ - methyl - *n*-octyl) - pyrrolidin - 3,5 - dione, or
2 - (6′ - Ethoxycarbonyl - *n* - hexyl) - 1 - (3″ - hydroxy - 3″ - methyl - *n*-decyl) - pyrrolidin - 3,5 - dione, or
2 - (6′ - Ethoxycarbonyl - *n* - hexyl) - 1 - (3″ - hydroxy - 3″ - ethyl - *n*-nonyl) - pyrrolidin - 3,5 - dione.

42. 2 - (6′ - Ethoxycarbonyl - *n* - hexyl) - 1 - (3″ - hydroxy - 3″ - methyl - *n*-nonyl) - pyrrolidin - 3,5 - dione.

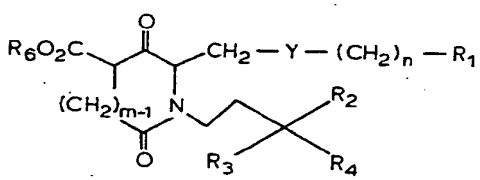
43. A process for the preparation of a compound of the formula (I) as defined in claim 1, which process comprises decarboxylating a compound of the formula (VI):



(VI)

wherein m, n, Y, R_1, R_2, R_3 and R_4 are as defined in formula (I), to yield a compound of the formula (I) wherein X and Z are CO, and thereafter if necessary converting X in the thus formed compound to protected CO by conventional methods, or to CROH by reduction when R is hydrogen or by reaction with a C_{1-4} alkyl Grignard reagent or C_{1-4} alkyl metallic complex when R is C_{1-4} alkyl, and then optionally protecting the CROH hydroxy moiety; and thereafter if necessary reacting a thus formed compound of the formula (I) wherein Z is CO with a vigorous reducing agent to convert it into the corresponding compound wherein Z is CH_2 and wherein other carbonyl functions present in the chosen compound of the formula (I) are reduced, and thereafter if necessary oxidising one or more of these reduced carbonyl groups back to carbonyl groups.

44. A process according to claim 46, wherein the compound of the formula (VI) is generated *in situ* from a corresponding ester of formula (VII):



(VII)

wherein CO_2R_6 is an ester group in which the ester moiety contains from 1 to 12 carbon atoms, and n, m, R_1, R_2, R_3, R_4 and Y are as defined in formula (I).

45. A process according to claim 44, substantially as hereinbefore described with reference to any one of the specific Examples 2 to 15.

46. A compound according to claim 1, whenever prepared by a process according to claim 43 or claim 44.

47. A compound according to claim 1, substantially as hereinbefore described with reference to any one of the specific Examples 2 to 15.

48. A pharmaceutical composition comprising a compound as defined in any one of the claims 1 to 14, 28 and 36, and a pharmaceutically acceptable filler.

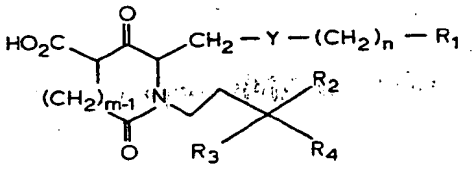
49. A pharmaceutical composition comprising a compound as defined in any one of the claims 15 to 27, 29 to 35 and 37 to 42, and a pharmaceutically acceptable filler.

50. A process for the preparation of a composition according to claim 48 and 49, which process comprises bringing together the compound of the formula (I) and pharmaceutically acceptable filler in known manner.

51. A method of treatment or prophylaxis of disorders in animals other than humans, which method comprises the administration of an effective amount of a compound of the formula (I) as claimed in any one of the claims 1 to 14, 28 and 36.

52. A method of treatment or prophylaxis of disorders in animals other than humans, which method comprises the administration of an effective amount of a compound of the formula (I) as claimed in any one of the claims 15 to 27, 29 to 35, and 37 to 42.

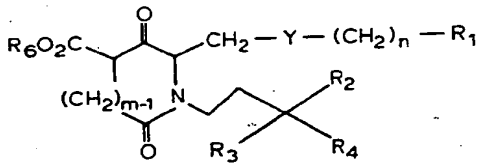
53. A compound of the formula (VI)



(VI)

wherein the variable groups are as defined is any one of the claims 1 to 27.

54. A compound of the formula (VII):



(VII)

wherein CO_2R_6 is an ester group in which the ester moiety contains from 1 to 12 carbon atoms, and the other variable groups are as defined in any one of the claims 1 to 27.

55. A compound according to claim 54, substantially as hereinbefore described with reference to Example 1.

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